Resting EEG theta connectivity and alpha power to predict repetitive transcranial magnetic stimulation response in depression

Citation for published version (APA):

Bailey, N. W., Krepel, N., van Dijk, H., Leuchter, A. F., Vila-Rodriguez, F., Blumberger, D. M., Downar, J., Wilson, A., Daskalakis, Z. J., Carpenter, L. L., Corlier, J., Arns, M., & Fitzgerald, P. B. (2021). Resting EEG theta connectivity and alpha power to predict repetitive transcranial magnetic stimulation response in depression: A non-replication from the ICON-DB consortium. *Clinical Neurophysiology*, 132(2), 650-659. <https://doi.org/10.1016/j.clinph.2020.10.018>

Document status and date:

Published: 01/02/2021

DOI:

[10.1016/j.clinph.2020.10.018](https://doi.org/10.1016/j.clinph.2020.10.018)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Resting EEG theta connectivity and alpha power to predict repetitive transcranial magnetic stimulation response in depression: A non-replication from the ICON-DB consortium

Neil W. Bailey^{a,b,*}, Noralie Krepel^{c,d}, Hanneke van Dijk^{c,j}, Andrew F. Leuchter^e, Fidel Vila-Rodriguez^f, Daniel M. Blumberger^{g,h}, Jonathan Downar^g, Andrew Wilson^e, Zafiris J. Daskalakis^{g,h}, Linda L. Carpenterⁱ, Juliana Corlier^e, Martijn Arns^{c,d,j,1}, Paul B. Fitzgerald^{a,b,1}

^a Epworth Centre for Innovation in Mental Health, Epworth Healthcare, The Epworth Clinic, Camberwell, Victoria 3004, Australia

^b Monash University, Department of Psychiatry, Central Clinical School, Commercial Rd, Melbourne, Victoria, Australia

^c Research Institute Brainclinics, Brainclinics Foundation, Nijmegen, the Netherlands

^d Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, the Netherlands

^e TMS Clinical and Research Program, Neuromodulation Division, Semel Institute for Neuroscience and Human Behavior at UCLA, Dept. of Psychiatry & Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

^f Non-Invasive Neurostimulation Therapies Laboratory, Dpt. Psychiatry, The University of British Columbia, Vancouver, BC, Canada

^g Dept. of Psychiatry, University of Toronto, Toronto, ON, Canada

^h Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, ON, Canada

ⁱ Butler Hospital Mood Disorders Research Program and Neuromodulation Research Facility, Dept. of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA

^j Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Location AMC, Amsterdam Neuroscience, the Netherlands

See Articles, pages 616–617, and 643–649

ARTICLE INFO

Article history:

Accepted 26 October 2020

Available online 10 November 2020

Keywords:

Replication

Alpha power

Theta connectivity

rTMS

Depression

ICON-DB

EEG

HIGHLIGHTS

- Baseline resting EEG theta connectivity and alpha power predicted response to rTMS for depression in our previous research.
- These measures did not differentiate responders and non-responders in a larger independent dataset.
- Theta connectivity and alpha power are unlikely to be clinically useful predictors of response to rTMS for depression.

ABSTRACT

Objective: Our previous research showed high predictive accuracy at differentiating responders from non-responders to repetitive transcranial magnetic stimulation (rTMS) for depression using resting electroencephalography (EEG) and clinical data from baseline and one-week following treatment onset using a machine learning algorithm. In particular, theta (4–8 Hz) connectivity and alpha power (8–13 Hz) significantly differed between responders and non-responders. Independent replication is a necessary step before the application of potential predictors in clinical practice. This study attempted to replicate the results in an independent dataset.

Methods: We submitted baseline resting EEG data from an independent sample of participants who underwent rTMS treatment for depression (N = 193, 128 responders) (Krepe et al., 2018) to the same between group comparisons as our previous research (Bailey et al., 2019).

Results: Our previous results were not replicated, with no difference between responders and non-responders in theta connectivity ($p = 0.250$, Cohen's $d = 0.1786$) nor alpha power ($p = 0.357$, $\eta_p^2 = 0.005$).

* Corresponding author at: Epworth Centre for Innovation in Mental Health, 888 Toorak Road, Camberwell, Victoria 3124, Australia.

E-mail address: neil.bailey@monash.edu (N.W. Bailey).

¹ Indicates shared senior author.

Conclusions: These results suggest that baseline resting EEG theta connectivity or alpha power are unlikely to be generalisable predictors of response to rTMS treatment for depression.

Significance: These results highlight the importance of independent replication, data sharing and using large datasets in the prediction of response research.

© 2020 International Federation of Clinical Neurophysiology. Published by Elsevier B.V. All rights reserved.

1. Introduction

Recently we published a study demonstrating accurate prediction of response to repetitive transcranial magnetic stimulation (rTMS) treatment for depression using machine learning (84% sensitivity and 89% specificity) of a number of resting electroencephalography (EEG) measures in combination with measures of early change in mood (Bailey et al., 2019). Differences between the responder and non-responder groups in the EEG measures of theta connectivity and alpha power were consistent at both baseline and after one week of treatment, suggesting these measures reflected stable traits that were related to treatment outcome. However, the dataset was comprised of 42 participants, with only 12 responders. While cross-validation was used to ensure results were not due to over-fitting in a small sample, and permutation tests showed the machine learning results were significantly more accurate than chance, independent replication of previous results is necessary to ensure findings are valid and reliable. In particular, independent replication of the successful prediction of response to rTMS is required before the results could be generalised to the broader population of depressed patients undergoing rTMS treatment (Widge et al., 2018). Successful replication of treatment response prediction is of significant clinical relevance, as rTMS results in distinct response or non-response outcomes, and rTMS treatments involve costly and time-consuming treatment regimens (Berlim et al., 2014; Fitzgerald et al., 2016; George and Post, 2011). Additionally, conducting a replication study also enables the testing of other possibly relevant variables that might influence the results. For example, previous results from Arns et al. (2016) indicated that frontal alpha asymmetry (FAA) was associated with response to selective serotonin reuptake inhibitors (SSRIs) in females only. The sample size of our original study was too small to enable interactions with sex to be tested (Bailey et al., 2019), but the results from Arns et al. (2016) demonstrate the importance of determining if interactions between response prediction variables and sex are present in order to enable maximum predictive accuracy.

To enable independent replications (as we aimed to perform) a large dataset ($N = 193$, with 128 responders) of baseline resting EEG data from an open-label trial of rTMS treatment of depression across two separate clinics was recently made available via a data sharing proposal (Krepel et al., 2018). Although minor differences between our original study and this replication dataset were present in data collection and processing (different depression severity assessment tools were used, different electrode montages, recording equipment and settings, absence of week 1 recordings, and different EEG pre-processing procedures) predictive variables should be robust to minor parameter variation to be clinically useful. We therefore deemed the data similar enough to enable an independent replication of the previous results.

We hypothesized that responders in the replication dataset would show higher theta connectivity from within the same group of electrode pairs that differentiated responders from non-responders in our original research (a broad group of electrode pairs involving frontal, parietal and occipital connections). Additionally, following research showing that predictors of response

can be sex specific (Arns et al., 2016), we had a non-directional hypothesis that the difference between responders and non-responders in theta connectivity would be influenced by sex. Following the results of our original research, we also hypothesized that responders would show less alpha power in frontal and occipital electrodes than non-responders, and responders would show a smaller difference in alpha power between frontal and occipital regions than non-responders. If these measures showed replication of the results from our original dataset, we hypothesized that a machine learning algorithm would show accurate response prediction from this baseline data, with similar specificity and sensitivity to our original dataset.

2. Methods

2.1. Participants

Participants with EEG recordings included 193 participants (95 male) with major depression aged 18–78 (Mean = 43.2, SD 12.9, which can be compared to the original dataset, with a Mean = 45.86, SD = 13.95) treated with simultaneous psychotherapy and rTMS (Mean = 20.9 sessions, SD 7.5). Participants were treated with either high frequency (10 Hz) left dorsolateral prefrontal cortex (DLPFC), low frequency (1 Hz) right DLPFC, or both sequentially (similar to our original research). Over 97% of the sample had at least one previous antidepressant treatment without response (in contrast to the original dataset, which only included participants who had tried at least two separate antidepressant treatments from different classes of antidepressants without response). Participants were separated into responders ($N = 128$) and non-responders ($N = 65$) defined by $\geq 50\%$ reduction in Beck Depression Inventory II Dutch Language Version (BDI-II-NL) score between baseline measurement and the final visit. Data from these participants has been previously reported, and further details of participant and treatment characteristics can be found in Donse et al. (2018). Power calculation using the effect size for differences in connectivity from Bailey et al. (2019) ($d = 1.097$) suggested 52 participants were necessary to obtain 0.95 power with an alpha of 0.05, and post-hoc power analysis showed the number of participants used provided >0.999 power. This demonstrated that the number of participants in the current study provided a more than large enough sample size to detect significant effects.

2.2. Electrophysiological recording and pre-processing

Two minutes of baseline resting EEG recordings with both eyes open (EO) and eyes closed (EC) were obtained using a 26 sintered Ag/AgCL electrode Quikcap (Neuroscan) and NuAmps amplifier (Compumedics, Neuroscan). Data was referenced online to averaged mastoids with a ground at FPz, impedances of <5 k Ω were maintained, and EEG activity was sampled at 500 Hz with a DC high pass and 100 Hz low pass filter. Horizontal eye movements were recorded by electrodes placed 1.5 cm lateral to the outer canthus of each eye, and vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid.

Offline data was processed using a standardized methodology (Arns et al., 2016, Arns et al., 2012). Data was bandpass filtered from 0.3 to 100 Hz with notch filters of 50 or 60 Hz (depending on which country data was recorded in) using zero phase Infinite Impulse Response filters. Eye movements were corrected using the Gratton and Coles method (Gratton et al., 1983). Data was epoched into two second windows across the recording period. Individual epochs per channel were automatically marked as artifact and rejected based on the following criteria: 1) A ratio of >0.375 for 30–90 Hz gamma power relative to the rest of the signal ratio, 2) the presence of shifts in the voltage slope from 16 consecutive samples that exceeded $25\times$ the epoch average, 3) kurtosis values >8 , 4) extreme frequency power in the epoch, with power values >350 from the summation of power in the 1–5.25 Hz range and the 22–45 Hz range after a Fast Fourier Transform of each epoch, scaled for electrode location by a linear increase in the threshold from 350 at the most anterior electrodes to 525 at the most posterior electrodes (as power is usually higher at posterior electrodes), 5) the presence of residual eye blink detection based on cross correlation values of >0.55 between eye electrodes and EEG electrodes, and 6) extreme voltage swing detection of $>200\ \mu\text{V}$ across the epoch. See Arns et al. (2016) for more details. Data was re-referenced to the average reference prior to analysis. All participants provided 35 or more noise free epochs for analysis from both eyes open and eyes closed conditions (mean = 56.7, SD = 1.8).

This can be compared with Bailey et al. (2019), who obtained three minutes of eyes open and eyes closed resting data for each participant using a 30 sintered Ag/AgCl electrode EasyCap (EasyCap, Woerthsee-Ettersschlag, Germany) and recording EEG activity using a Synamps 2 amplifier (Compumedics, Neuroscan). CPz was used as the online reference and AFz as the ground, impedances of $<5\ \text{k}\Omega$ were maintained, and EEG activity was sampled at 10,000 Hz with a DC high pass and 2000 Hz low pass filter. Horizontal eye movements were recorded by electrodes placed 1.5 cm lateral to the outer canthus of each eye, and vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid.

Data was processed using MATLAB (The Mathworks, Natick, MA) and EEGLAB (scn.ucsd.edu/eeqlab) (Delorme and Makeig, 2004). Data were initially downsampled to 1000 Hz, then second order butterworth filtering was applied with a bandpass from 1 to 80 Hz and a band stop filter from 47 to 53 Hz. Data was epoched into two second windows across the recording period with a 500 ms overlap. Single electrodes containing artifacts in more than 3% of epochs were rejected (indicated by variations in voltage that were larger than $250\ \mu\text{V}$, kurtosis values >5 , or values exceeding -100 or $30\ \text{dB}$ in the 25–45 Hz range). Epochs containing artifacts were also rejected (indicated by kurtosis values >3 for all electrodes or >5 for single electrodes, and more than -100 to $30\ \text{dB}$ in the 25–45 Hz range). Artifact rejections were manually verified by visual inspection by an experienced EEG researcher (NWB), then Fast independent component analysis (FastICA) (Hyvarinen, 1999, Hyvarinen and Oja, 2000) was used to manually select and remove eye blinks and movements and remaining muscle activity artefacts. The ‘symmetric approach’ and the ‘tanh’ contrast function were used for the algorithm. Recordings were re-referenced offline to an averaged reference. All participants provided 63 or more noise free epochs for analysis from both eyes open and eyes closed conditions.

To summarize the differences in the EEG recording and processing of the two datasets: 1) The replication dataset used a Quickcap and NuAmps amplifier while the original dataset used an EasyCap and Neuroscan Synamps 2 amplifier (as far as we are aware, these amplifiers are highly compatible). 2) The data were recorded at a

different sampling rate (the replication dataset recorded at 500 Hz while the original dataset recorded at 10,000 Hz and downsampled to 1000 Hz for analysis). 3) The data were processed using different methods. In the replication dataset (Krepel et al., 2018), epochs were rejected through a six step automated process that excluded epochs showing excessive power, kurtosis and voltage shift values, and eye blinks and movements were corrected using the Gratton and Coles method (Gratton et al., 1983), which corrects for this activity in the EEG trace without rejecting epochs contaminated by eye blink and movement. In the original study (Bailey et al., 2019), epoch rejection was based on kurtosis values of >5 in single electrodes or >3 for all electrodes, or power exceeding -100 to $30\ \text{dB}$ in the 25–45 Hz range, and FastICA (Hyvarinen, 1999, Hyvarinen and Oja, 2000) was used to manually select and remove components containing eye blinks, movements, and remaining muscle activity artefacts, which corrects for this activity in the EEG trace without rejecting epochs contaminated by eye blink and movement. 4) After extracting the significant group of electrode pairs from our previous research and applying that group of electrode pairs to the replication dataset (Krepel et al., 2018), we were left with only 14 electrode pairs in the proposed group of electrode pairs, compared to 66 electrode pairs in the network that differentiated responders and non-responders in the original research. However, when we re-analysed the original dataset using theta connectivity values from only the restricted montage and compared this group of electrode pairs between responders and non-responders, differences were still highly significant in that original dataset. This suggests that the restricted montage does not explain the lack of differences in the replication dataset.

2.3. Alpha power and theta connectivity computation

In order to determine whether our previous results replicated in this independent dataset, alpha power and theta connectivity values were computed by an independent team (NK and HvD) in the same manner as our previous research (Bailey et al., 2019). For the connectivity computation, EEG data was submitted to a single Hanning taper time-frequency transform, determining instantaneous phase values for the complex Fourier-spectra from 1 to 45 Hz with a 0.5 Hz resolution across sliding time windows corresponding to 4 cycles in length. These values were slightly higher than the original study, which used 1 Hz resolution across sliding time windows corresponding to 3 oscillation cycles in length. As such, the replication connectivity measures were assumed to be more robust than the original measures. The weighted phase lagged index (wPLI) was then calculated between each electrode to measure phase synchronisation between electrodes (Vinck et al., 2011). Following this, wPLI values in the theta frequency (4–8 Hz) were averaged across these frequencies, and across epochs in preparation for statistical analysis. Total average theta wPLI was also computed across all available electrode pairs in the group of electrode pairs that differentiated responders and non-responders in our original study. Not all electrodes from the original significant group of electrode pairs were present in the replication dataset, so the original dataset was tested on this reduced group of electrode pairs to confirm those results were not altered by reducing the number of electrode pairs included in the analysis (reported below). Electrode pairs that were both significantly different between responders and non-responders in the original study, and present in the replication dataset were Fz-FC4, FC3-FC4, F3-P3, FC3-P3, P3-P4, F3-O1, FC3-O1, P3-O1, P4-O1, F3-O2, FC3-O2, P3-O2, P4-O2, and O1-O2.

Alpha power was computed using a multi-taper fast Fourier frequency transformation with a Hanning taper to calculate power in the alpha range (8–13 Hz). Alpha power was calculated across each epoch, then averaged across the frequency window, across all epochs, and across both eyes open and eyes closed recordings, in

exact replication of the procedure from Bailey et al. (2019). As per our previous research, F3, F4, O1 and O2 electrodes were selected for analysis.

2.4. Statistical analysis

Traditional frequentist statistical comparisons were conducted using SPSS version 23. Bayesian comparisons were conducted using JASP version 0.11.1 (Love et al., 2019) to provide an indicator of the strength of evidence for null results. Where our previous results suggested directional finding that we would expect for the results in the current study, one-tailed Bayesian comparisons were used, as a result in the opposite direction would provide the same rejection of our previous conclusion as no difference between groups (Ruxton and Neuhäuser, 2010). For analyses involving more than a single factor, comparisons were made between Bayesian models containing a hypothesized effect to equivalent models stripped of the effect. Comparisons of connectivity values across all electrodes were performed using the network based statistics (NBS) (Zalesky et al., 2010). In order to confirm the comparisons of theta connectivity made using the reduced electrode montage available in the replication data was still a valid test of our initial result, we conducted an independent samples t-test of averaged wPLI values from electrode pairs that were both within the group of electrode pairs that significantly differentiated responders and non-responders shown in our initial study, and present in the electrode montage from the replication study. Next, to test our primary hypothesis of replication of increased theta connectivity in responders within the same group of electrode pairs as the original research, we performed an independent samples t-test comparing responders and non-responders in averaged theta wPLI values across the group of electrode pairs including electrode pairs common to both studies and averaged across EO and EC conditions. In order to test whether the original result might also be specific to a stimulation type, we performed a sub-analysis with the same t-test but restricted to only participants who underwent 10 Hz left side treatment. To test our hypothesis that sex would influence these results, we also performed a repeated measures ANOVA on averaged theta wPLI values from this group of electrode pairs using group (responder and non-responder) and sex (females and males) as between-subject factors and condition (EO and EC) as the within-subject factor, with age as a covariate. Thirdly, in order to assess connectivity across all electrodes (in case a different group of electrode pairs separated responders and non-responders in the replication sample) we submitted the replication dataset to a t-test comparison of responders and non-responders using the NBS cluster analysis of connectivity values across all pairs of electrodes available in the replication dataset (Zalesky et al., 2010). Finally, the last comparison of theta connectivity administered this same NBS test separately for each sex. Note that Bayesian statistics are not currently able to replicate the analyses performed by the NBS, so we were unable to test for the strength of our conclusion with regards to the analysis including all pairs of electrodes. In order to assess alpha power differences between responders and non-responders, we conducted a repeated measures ANOVA including group (responder and non-responder) and sex (females and males) as between-subject factors, with hemisphere (right and left), and region (frontal [F3, F4] and occipital [O1, O2]) as within-subject factors, and age as a covariate. We also conducted this analysis restricted to participants who underwent 10 Hz left sided treatment. As reported below, our results were non-significant, so no machine learning algorithm was applied.

3. Results

Clinical results from the dataset have been reported previously (Donse et al., 2018). When the averaged wPLI values from the original study were restricted to just the electrodes that overlapped between the two labs, comparisons between responders and non-responders were still significant $t(40) = 2.824$, $p = 0.015$, Cohen's $d = 1.0968$ (responder mean = 0.0901 SD = 0.0667, non-responder mean = 0.0338, SD = 0.0286). However, in the replication dataset, no significant difference was found in averaged connectivity from within the same group of electrode pairs as the original study between responders ($M = 0.02279$, $SD = 0.02240$) and non-responders ($M = 0.02825$, $SD = 0.02083$), $t(191) = 1.638$, $p = 0.103$, Cohen's $d = 0.25241$, $BF_{0-} = 15.132$ (see Fig. 1). Additionally, even though the result was not significant and showed a small effect size, the effect was in the opposite direction to the original study. The sub-analysis focusing on only participants who underwent 10 Hz left side treatment also showed no differences between responders ($M = 0.02123$, $SD = 0.01790$) and non-responders ($M = 0.02577$, $SD = 0.01753$), $t(71) = 1.013$, $p = 0.314$, Cohen's $d = 0.255$, $BF_{0-} = 7.101$. Furthermore, there was neither an interaction between response-group and sex, nor response-group, sex and eyes open or closed (all $p > 0.10$ and $BF_{\text{excl}} > 3$, see table 1 for detailed statistics). An interaction was observed between age and EO or EC, $F(1,189) = 5.141$, $p = 0.025$, $\eta_p^2 = 0.027$, such that age positively correlated with EC connectivity $r(193) = 0.237$, $p = 0.001$ but not EO connectivity $r(193) = 0.082$, $p = 0.255$. Using NBS to compare across all pairs of electrodes in the replication dataset revealed no differences between responders and non-responders, nor differences when data was split by sex (all $p > 0.05$), similar to the analyses performed in SPSS.

Alpha power comparisons also showed no differences between responders and non-responders $F(1,189) = 0.851$, $p = 0.357$, $\eta_p^2 = 0.005$, $BF_{\text{excl}} = 4.086$ (see Fig. 2, details in table 2). There was also no interaction between response-group and electrode region $F(1,189) = 0.578$, $p = 0.448$, $\eta_p^2 = 0.003$, $BF_{\text{excl}} = 6.880$. The main response-group effect was not influenced by sex $F(1,189) = 0.303$, $p = 0.582$, $\eta_p^2 = 0.002$, $BF_{\text{excl}} = 3.529$, nor was the interaction between response-group, sex, and electrode region $F(1,189) = 0.037$, $p = 0.848$, $\eta_p^2 < 0.001$, $BF_{\text{excl}} = 3.580$. Lastly, there was no interaction between hemisphere, region, sex and response-group $F(1,189) = 0.008$, $p = 0.927$, $\eta_p^2 < 0.001$, $BF_{\text{excl}} = 4.312$. When performing the same comparisons restricted to participants who underwent 10 Hz left-sided rTMS, we likewise observed no differences (see Fig. 3, all $p < 0.2$, $BF_{\text{excl}} > 2$, details in table 3). All data met the assumption of equal variances (all $p > 0.2$).

4. Discussion

The aim of this study was to determine whether our previous research demonstrating that responders to rTMS treatment for depression showed higher resting EEG theta connectivity and lower alpha power than non-responders (Bailey et al., 2019) would replicate in a larger independent sample (Krepel et al., 2018), indicating clinical relevance and applicability of these measures. The results of this study did not replicate our previous research as we did not observe similar differences between the responders and non-responders. Furthermore, although the selected measures did not differ between response-groups, the pattern for theta connectivity was reversed compared to our original results (with non-responders showing higher values), strongly suggesting our original finding does not generalise. Additionally, we aimed to assess whether our previous results would be modified by including sex in the analyses, as previous research has indicated that predictors of response may be modulated by sex (Arns et al., 2016). As with

Fig. 1. Mean theta (4–8 Hz) weighted phase lag index (wPLI) connectivity values from responder and non-responder groups in the replication dataset (error bars reflect standard deviations). No significant differences were detected between responders and non-responders, in contrast to the original dataset and our hypotheses.

Table 1

Mean values for resting wPLI theta connectivity, standard deviations and statistical comparisons between responders and non-responders in the replication data (values averaged across the group of electrode pairs that differentiated responders and non-responders in the original research, excluding electrode pairs that did not overlap between the two studies). EO = eyes open, EC = eyes closed. SD = standard deviation.

Measurement	Responders Mean (SD)		Non-Responders Mean (SD)		Statistics
	Females (N = 69)	Males (N = 59)	Females (N = 29)	Males (N = 36)	
EO	0.0165 (0.0211)	0.0132 (0.0115)	0.0197 (0.0189)	0.0168 (0.0170)	Between group comparison: $t(191) = 1.638$, $p = 0.103$, Cohen's $d = 0.2524$, $BF_{0-} = 15.132$ Interaction between group and sex: $F(1,188) = 2.001$, $p = 0.159$, $\eta_p^2 < 0.011$, $BF_{excl} = 4.062$ Interaction between group, sex and eyes: $F(1,188) = 1.061$, $p = 0.304$, $\eta_p^2 < 0.006$, $BF_{excl} = 3.588$
EC	0.0273 (0.0302)	0.0345 (0.0425)	0.0384 (0.0406)	0.0384 (0.0325)	

Fig. 2. Mean alpha power values from responder and non-responder groups in the replication dataset (error bars reflect standard deviations). No significant differences were detected between responders and non-responders, nor interaction between region and response-group, in contrast to the original dataset and our hypotheses.

Table 2

Resting alpha power means, standard deviations and statistical comparisons between responders and non-responders in the replication data. SD = standard deviation.

Electrode	Responders Mean (SD)		Non-Responders Mean (SD)		Statistics
	Females (N = 69)	Males (N = 59)	Females (N = 29)	Males (N = 36)	
F3	4.31 (3.30)	4.38 (3.90)	5.66 (4.40)	3.76 (2.65)	Between group comparison: $F(1,189) = 0.851$, $p = 0.357$, $\eta_p^2 = 0.005$, $B_{Fexcl} = 4.086$ Interaction between group and region: $F(1,189) = 0.578$, $p = 0.448$, $\eta_p^2 = 0.003$, $B_{Fexcl} = 6.880$ Interaction between group and sex: $F(1,189) = 0.303$, $p = 0.582$, $\eta_p^2 = 0.002$, $B_{Fexcl} = 3.529$ Interaction between group, sex and region: $F(1,189) = 0.037$, $p = 0.848$, $\eta_p^2 < 0.001$, $B_{Fexcl} = 3.580$ Interaction between group, sex, region and hemisphere: $F(1,189) = 0.008$, $p = 0.927$, $\eta_p^2 < 0.001$, $B_{Fexcl} = 4.312$
F4	4.33 (3.27)16.27	4.35 (3.90)16.01	5.65 (4.42)20.46	4.01 (2.78)14.75	
O1	(13.66)16.12	(23.62)15.14	(24.13)	(12.15)13.82	
O2	(15.69)	(20.24)	20.32 (23.35)	(11.68)	

Fig. 3. Mean alpha power values from responder and non-responder groups in the replication dataset for participants who underwent 10 Hz left hemisphere repetitive transcranial magnetic stimulation (rTMS) treatment only (error bars reflect standard deviations). As with the full dataset, no significant differences were detected between responders and non-responders.**Table 3**

Resting alpha power means, standard deviations and statistical comparisons between responders and non-responders to 10 Hz left sided treatment only in the replication data. SD = standard deviation.

Electrode	Responders Mean (SD)		Non-Responders Mean (SD)		Statistics
	Females (N = 25)	Males (N = 25)	Females (N = 11)	Males (N = 12)	
F3	3.23 (2.22)	4.73 (3.47)	5.07 (3.63)	2.34 (1.66)	Between group comparison: $F(1,68) = 0.026$, $p = 0.872$, $\eta_p^2 < 0.001$, $B_{Fexcl} = 3.647$ Interaction between group and region: $F(1,68) = 0.048$, $p = 0.827$, $\eta_p^2 = 0.001$, $B_{Fexcl} = 4.220$ Interaction between group and sex: $F(1,68) = 0.675$, $p = 0.414$, $\eta_p^2 = 0.010$, $B_{Fexcl} = 2.090$ Interaction between group, sex and region: $F(1,68) = 0.017$, $p = 0.896$, $\eta_p^2 < 0.001$, $B_{Fexcl} = 2.637$ Interaction between group, sex, region and hemisphere: $F(1,68) = 0.307$, $p = 0.581$, $\eta_p^2 < 0.004$, $B_{Fexcl} = 3.245$
F4	3.29 (2.11)	4.48 (3.20)	4.76 (3.00)	2.89 (2.69)	
O1	14.26 (12.20)	17.58 (14.19)	17.32 (16.24)	12.49 (10.63)	
O2	16.73 (17.50)	17.80 (16.65)	17.49 (18.82)	13.31 (12.11)	

the main comparisons, no interaction between sex and theta connectivity or alpha power were found. These results were also consistent when analyses were restricted to participants receiving 10 Hz left sided treatment only. The results suggest that our previous findings do not generalise to independent samples, and as such the particular resting theta connectivity and resting alpha power measures examined in this study are unlikely to be clinically useful biomarkers for response to rTMS treatment for depression.

The non-replication was unexpected. In the original dataset (Bailey et al., 2019), the theta connectivity differences between responders and non-responders were present in comparisons across both baseline and week 1 time-points, suggesting a robust effect. Machine learning predictions including theta connectivity and alpha power were also accurate across learning and test samples. This consistency, comprised of test-retest replication across time and within sample replication across divisions of the same

Table 4

Summary of parameters that were the same or differed between the datasets.

Parameter	Bailey et al. (2019)	Krepel et al. (2018)	Same/Different?	Explains Results?
Electrode montage	30 electrodes	26 electrodes	F3, Fz, F4, FC4, FCz, FC3, P3, Pz, P4, O1, O2 were present in both studies, other electrodes differed	No - limiting comparisons of original dataset to only include overlapping electrodes did not alter results
EEG Amplifier	Neuroscan Synamps 2	Neuroscan NuAmps	Same chipset	Very unlikely to explain results
EEG Sampling Rate	10,000 Hz downsampled to 1000 Hz	500 Hz	Different	No reason to believe this would explain results
EEG Artifact Rejection	Epoch rejection via kurtosis values or excessive power in the 25–45 Hz range, FastICA to reject eye movements and other remaining artifacts	Epochs rejected following a 6-step automated process rejecting high kurtosis and power values, eye movements corrected using the Gratton and Coles method	Different, but both methods remove artifacts and use methods to correct for eye blinks and movements (rather than simply delete these artifacts)	No reason to believe this would explain results
Depression Severity	HDRS	BDI-II-NL	Different, but highly correlated	No reason to believe this would explain results
Treatment Resistance	Failure to respond to at least two antidepressants from two separate classes	97% of the sample showed failure to respond to at least one antidepressant	Different	Possible – but if it explains results then predictive potential of the original study is limited to a specific population
rTMS treatment	3 weeks of 10 Hz left DLPFC rTMS, then randomised to continue for 3 weeks, or to 1 Hz right DLPFC, or bilateral rTMS. 110% of RMT	10 Hz left DLPFC, 1 Hz right DLPFC, or bilateral, >10 sessions for inclusion, 110–120% of RMT	The minimum number of rTMS treatments for inclusion from Bailey et al. (2018) was higher, otherwise parameters were highly similar	No reason to believe this would explain results
Concurrent therapy	Antidepressants, and a minority of participants taking additional mood stabilisers, antipsychotics, or no medications	Cognitive Behaviour Psychotherapy, medications not recorded	Different	Unclear
Sample size	42 (12 responders)	193 (128 responders)	Different	Possible – replication dataset is a more generalized sample, original dataset may contain sampling bias
Age	Mean 45.86, SD = 13.95	Mean 43.2, SD = 12.9	Very similar	Unlikely to explain results

DLFPC: dorsolateral pre-frontal cortex, rTMS: repetitive transcranial magnetic stimulation, HDRS: Hamilton Depression Rating Scale, BDI-II-NL: Beck Depression Inventory II - Dutch version.

sample, suggested that differences were likely to reflect genuine findings. However, the results do not replicate, which prompts the question of why our results seemed to show consistency within the study, but not in data obtained and processed by other researchers.

There were a number of differences between the two datasets in response definition, treatment resistance definition, EEG recording, and EEG pre-processing steps (summarized in Table 4). Perhaps most importantly, the specific electrode locations used differed between the two studies. However, when we re-analysed the original dataset using theta connectivity values from only the restricted montage that overlapped with the replication dataset, and compared this group of electrode pairs between responders and non-responders, differences were still highly significant in that original dataset. This suggests that the restricted montage does not explain the lack of differences in the replication dataset. Secondly, the two datasets were recorded using different (but highly similar) amplifiers, sampling rates, and were pre-processed using different artefact rejection / correction procedures. Thirdly, the inclusion criteria involving treatment resistance differed between the two studies. The original dataset (Bailey et al., 2019) used an inclusion criterion of at least two failed antidepressant treatments from different classes of antidepressants, while the replication dataset (Krepel et al., 2018) did not have a formal inclusion criterion around treatment resistance (although 97% of participants had at least one failed antidepressant treatment). This point suggests that the replication dataset is likely to consist of a more heterogeneous sample with a broader range of treatment resistance. If the measures that predicted response in the original dataset are influenced by the severity of treatment resistance, this difference between the datasets could offer an explanation for the inconsistency between the two studies. However, we think it is unlikely that the inclusion of less treatment resistant participants would have reversed the pattern of theta connectivity, as this would suggest that individuals who had only tried one unsuccessful antidepressant would show the opposite relationship between theta connectivity at baseline and treatment response compared to individuals who had tried two or more antidepressants.

Additionally, while participants in the original dataset (Bailey et al. 2019) were mostly taking antidepressants (and also mood stabilisers or antidepressants, or no medications in a small number of cases), the replication dataset (Krepel et al. 2018) was a naturalistic sample so did not obtain verified data on medication use. However, recent research examining frontal alpha asymmetry has shown the measure could accurately predict response both prior to and after SSRI treatment, suggesting that successful prediction of treatment response with EEG measures is likely to be robust to differences in medication status (van der Vinne et al., 2019). Lastly, the two samples measured depression severity (and as such defined response to treatment) using different scales. The original research (Bailey et al., 2019) used the Hamilton Depression Rating Scale (HDRS), while the replication dataset (Krepel et al., 2018) used the BDI-II-NL (with both studies defining response as a 50% reduction from baseline scores to endpoint). However, there is no indication that the different measures have a different relationship to the EEG measures, and the two depression severity measures have been shown to be highly correlated (Fitzgibbon et al., 1988). As such, none of the differences in response definition, EEG recording, or EEG pre-processing steps suggest to us an obvious confound that would have led to systematic differences between responders and non-responders in theta connectivity or alpha power. Additionally, for our findings to be generalizable and clinically useful, they should be robust against minor variations in data collection or pre-processing, and generalizable to patients across a broad range of inclusion criteria.

In addition to the differences in data measurement between the two datasets, the participants in the replication dataset (Krepel et al., 2018) underwent cognitive behaviour psychotherapy concurrently with rTMS treatment, while participants in the original dataset (Bailey et al., 2019) did not. It is likely that psychotherapy treats depression through a mechanism that is different to rTMS, and it is possible that the mechanism underpinning psychotherapy is unrelated to theta connectivity or alpha power at baseline (or even related to theta connectivity / alpha power at baseline, but in the opposite direction to the direction shown with rTMS in our original study). While we were unable to find research directly addressing the relationship between theta connectivity or alpha power and response to psychotherapy, a review drawing evidence from parallel studies of psychotherapy and rTMS has suggested that the two therapies target different mechanisms within emotional processing networks (Thase, 2014), with intact executive function being suggested to predict response to psychotherapy (Harmer, 2014). Additionally, low levels of rostral and subgenual cingulate activity has been proposed by a theoretical perspective to be a predictor for psychotherapy response (DeRubeis et al., 2008), whereas high levels of anterior cingulate activity and high resting fMRI anti-correlations between subgenual cingulate activity and the left prefrontal cortex have been shown to predict response to rTMS (Baeken et al., 2014, Fox et al., 2012, Langguth et al., 2007). If psychotherapy and rTMS do act via different mechanisms that are relevant to theta connectivity and alpha power, the effect of psychotherapy in the replication dataset may have diluted the statistical signal in the predictive relationship between theta connectivity, alpha power, and response, offering a potential explanation for the non-replication. However, there is no direct evidence to support the proposition that the presence of psychotherapy eliminated the statistical signal for theta connectivity and alpha power in the replication dataset. Given the fact that the pattern for theta connectivity was reversed in the replication dataset, we think the most parsimonious explanation is simply that the pattern from the original dataset (Bailey et al., 2019) was specific to that sample, but does not generalise to the broader population of individuals undergoing rTMS treatment for depression. Despite this conclusion based on parsimony, it may be valuable for future research to examine theta connectivity and alpha power measures as predictors of rTMS treatment without concurrent cognitive behaviour psychotherapy.

A final difference between the two datasets is unrelated to the current results, but may be relevant for future research to consider. While the replication dataset only contained resting EEG, the original dataset additionally included working memory related EEG (which was reported in Bailey et al. 2018). In addition to the higher resting theta connectivity, responders in the original dataset also showed higher working memory related theta connectivity (Bailey et al., 2018). While the replication sample demonstrated that resting theta connectivity differences between responders and non-responders did not generalise to an independent sample, they do not demonstrate the same for working memory related theta connectivity. However, given the responders in the original dataset showed higher theta connectivity across both baseline and week 1 measures that were consistent across the resting EEG and the working memory EEG, we think it is likely the higher theta connectivity reflects a phenotype in those participants that is common across both resting and cognitive processes (note that the resting EEG recordings were performed prior to the working memory EEG, so our resting results were not influenced by a delayed cognition related increase in theta connectivity). As such, if our assumption that the higher theta connectivity was specific to that sub-set of responders is accurate, then we think it would be unlikely that higher theta connectivity related to working memory could predict responders in independent samples.

As such, because there are no measurement or treatment differences between the two datasets that offer obvious explanations for the non-replication, our interpretation of the two studies is that the 12 responders in our original research showed trait higher connectivity values on average merely by chance, and this may have been due to an unspecified sampling bias which was not apparent in the much larger replication dataset that included 128 responders. The higher theta connectivity as a trait in these individuals explains the consistency across both baseline and week 1 recordings in the original research (Bailey et al., 2019) as well as the working memory EEG measures (Bailey et al., 2018), but a potential unspecified sampling bias in the original dataset would explain the non-replication when examining the replication dataset (Krepel et al., 2018). The proposition that depression is likely to be comprised of multiple underlying phenotypes (Insel and Wang, 2010; Widge et al., 2017) is one possible explanation. It may be that some of these phenotypes respond to rTMS while others do not, in which case knowing a patient's phenotype may lead to response prediction (Drysdales et al., 2017, however, also see Dinga et al., 2019). As such, it may be that smaller sample sizes that may be less representative of the broad population contain more of certain depression phenotypes, leading to apparently high prediction accuracy which does not replicate when using a more representative sample containing the full spectrum of phenotypes. This suggests that research examining response prediction may be more complicated than simply finding a biomarker that can be used across all patients (Insel and Wang, 2010; Widge et al., 2017).

Although the non-replication means the particular theta connectivity and alpha power measures in this study may not have clinical utility, the result is valuable, as it narrows the search space for potential predictors of rTMS response by process of elimination. Non-replication studies are particularly important to publish, as the robustness and reliability of prediction studies is questionable, and publication bias has been demonstrated in the prediction of depression treatment response literature (Widge et al., 2019). Rigorous methodology and reporting as well as replication attempts have been proposed as the solution to this issue (Widge et al., 2019). Additionally, while resting theta connectivity and resting alpha power appear not to be generalisable predictors of response to rTMS, a number of measures have been replicated both by our original research and other labs. In particular, proximity of the alpha frequency to the 10 Hz rTMS stimulation frequency, as reported by Corlier et al. (2019) was successfully replicated by this ICON-DB consortium (Roelofs et al., n.d.) and early change in mood showed the largest effect size for differences between responders and non-responders of the measures in our original research (Bailey et al., 2019) and in other research (Donse et al., 2018). Early change in cognitive performance also seems to be a replicable predictor, particularly early change in working memory performance (Bailey et al., 2018; Hoy et al., 2012). Also, fronto-midline theta during a working memory task was shown to differentiate responders and non-responders in the original sample (Bailey et al., 2019) even though fronto-midline theta during resting EEG did not differentiate the two groups. Fronto-midline theta has been suggested to be related to attention and cognitive control, to be generated by the anterior cingulate cortex, and to be negatively correlated with default mode network activity, all of which are implicated in depression (Nigbur et al., 2011; Onton et al., 2005; Pizzagalli et al., 2001; Sauseng et al., 2007; Scheeringa et al., 2008). Task related EEG has the added benefit of showing good test-retest reliability, increasing its potential utility as a predictor (Tenke et al., 2017). As such, we suggest that cognition related fronto-midline theta activity is also worth further exploration as a potential predictor (however, see Haller et al. (2018) for methods to ensure oscillation measurements are not confounded by non-oscillatory activity).

In addition to the recommendations for potential biomarkers in future research, we would also recommend that future research examining connectivity use multiple measures of connectivity, as recent reviews have suggested the use of a single connectivity measure may either fail to reveal true connectivity or falsely identify connectivity in the absence of connectivity differences (Bakhshayesh et al., 2019). While the wPLI measure of connectivity we used is one of the measures least affected by the volume conduction of artefacts of all connectivity measures (Anastasiadou et al., 2019), and the consistency across time and within the sample in our original research suggests true connectivity differences in that sample which were detected using the wPLI method (but do not generalise external to the sample), the point still stands that future research will be able to more rigorously test connectivity as a potential predictor using multiple measures.

To conclude, the current study indicated that resting EEG measures of alpha power and theta connectivity which predicted response to rTMS treatment for depression did not replicate in a large independent sample. This suggests that other measures are more likely candidates for prediction of response and demonstrates the importance of replication research.

Declaration of Competing Interest

MA is unpaid research director of the Brainclinics Foundation, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications related to EEG, neuromodulation and psychophysiology, but receives no royalties related to these patents; Brainclinics Foundation received research funding from Brain Resource (Sydney, Australia), Urgotech (France) and neuroCare Group (Munich, Germany), and equipment support from Deymed, neuroConn, Brainsway and Magventure.

FVR receives research support from Canadian Institutes of Health Research, Brian Canada, Michael Smith Foundation for Health Research, Vancouver Coastal Health Research Institute, and in-kind equipment support for investigator-initiated trial from MagVenture. He has participated in an advisory board for Janssen.

PBF is supported by a NHMRC Practitioner Fellowship (1078567). PBF has received equipment for research from MagVenture A/S, Medtronic Ltd, Neuronetics and Brainsway Ltd and funding for research from Neuronetics. He is on scientific advisory boards for Bionomics Ltd and LivaNova and is founder of TMS Clinics Australia.

AFL discloses that he has received research support from NIH, Neuronetics, Breast Cancer Foundation, Department of Defense, CHDI Foundation, and Neurosigma. He has served as a consultant to Ionis Pharmaceuticals, CHDI Foundation, and NeoSync, Inc. He is Chief Scientific Officer of Brain Biomarker Analytics LLC (BBA). He has stock options in NeoSync, Inc. and equity interest in BBA.

DMB has received research support from the CIHR, NIH, Brain Canada and the Temerty Family Foundation through the CAMH Foundation and the Campbell Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd., and he is the principal site investigator for three sponsor-initiated studies for Brainsway Ltd. He received in-kind equipment support from Magventure for investigator-initiated research. He received medication supplies for an investigator-initiated trial from Indivior. He has participated in an advisory board for Janssen.

LLC discloses that she has received research support from NIH, Neuronetics, Nexstim, Janssen, Neosync, and Affect Neuro. She has received consulting income from Janssen and Affect Neuro.

In the last 5 years, ZJD has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. His work was supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of

Health Research (CIHR), the National Institutes of Mental Health (NIMH) and the Temerty Family and Grant Family and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute.

JC, NK, HvD, NWB, and CR have nothing to disclose.

Acknowledgments

This report forms the second communication of the 'International Consortium On Neuromodulation – Discovery of Biomarkers (ICON-DB)', which was established during the 3rd International Brain Stimulation Conference held in Vancouver in 2019. A group of EEG and TMS researchers decided to initiate this consortium in order to facilitate direct replication of EEG and TMS-EEG findings by facilitating immediate and independent cross-dataset replication in order to foster robustness of research findings and facilitate translation into clinical practice. Requests for replication studies can be emailed to Andrew Leuchter (afl@ucla.edu) or Martijn Arns (martijn@brainclinics.com).

References

- Anastasiadou MN, Christodoulakis M, Papanthanasios ES, Papacostas SS, Hadjipapas A, Mitsis GD. Graph theoretical characteristics of EEG-based functional brain networks in patients with epilepsy: the effect of reference choice and volume conduction. *Front Neurosci* 2019;13:221.
- Arns M, Bruder G, Hegerl U, Spooner C, Palmer DM, Etkin A, et al. EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. *Clin Neurophysiol* 2016;127(1):509–19.
- Arns M, Drinkenburg WH, Fitzgerald PB, Kenemans JL. Neurophysiological predictors of non-response to rTMS in depression. *Brain Stimul* 2012;5(4):569–76.
- Baeken C, Marinazzo D, Wu G-R, Van Schuerbeek P, De Mey J, Marchetti I, et al. Accelerated HF-rTMS in treatment-resistant unipolar depression: insights from subgenual anterior cingulate functional connectivity. *World J Biol Psychiatry* 2014;15(4):286–97.
- Bailey N, Hoy K, Rogasch N, Thomson R, McQueen S, Elliot D, et al. Responders to rTMS for depression show increased fronto-midline theta and theta connectivity compared to non-responders. *Brain Stimul* 2018;11(1):190–203.
- Bailey N, Hoy K, Rogasch N, Thomson R, McQueen S, Elliot D, et al. Differentiating responders and non-responders to rTMS treatment for depression after one week using resting EEG connectivity measures. *J Affect Disord* 2019;242:68–79.
- Bakhshayesh H, Fitzgibbon SP, Janani AS, Grummett TS, Pope KJ. Detecting synchrony in EEG: A comparative study of functional connectivity measures. *Comput Biol Med* 2019;105:1–15.
- Berlim M, Van den Eynde F, Tovar-Perdomo S, Daskalakis Z. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med* 2014;44(2):225–39.
- Corlier J, Carpenter LL, Wilson AC, Tirrell E, Gobin AP, Kavanaugh B, et al. The relationship between individual alpha peak frequency and clinical outcome with repetitive Transcranial Magnetic Stimulation (rTMS) treatment of Major Depressive Disorder (MDD). *Brain Stimul* 2019;12(6):1572–8.
- Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004;134(1):9–21.
- DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nat Rev Neurosci* 2008;9(10):788–96.
- Dinga R, Schmaal L, Penninx BW, van Tol MJ, Veltman DJ, van Velzen L, et al. Evaluating the evidence for biotypes of depression: Methodological replication and extension of. *NeuroImage: Clin* 2019;22:101796.
- Donse L, Padberg F, Sack AT, Rush AJ, Arns M. Simultaneous rTMS and psychotherapy in major depressive disorder: Clinical outcomes and predictors from a large naturalistic study. *Brain Stimul* 2018;11(2):337–45.
- Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* 2017;23(1):28.
- Fitzgerald PB, Hoy KE, Anderson RJ, Daskalakis ZJ. A study of the pattern of response to rTMS treatment in depression. *Depress Anxiety* 2016;33(8):746–53.
- Fitzgibbon ML, Cella DF, Sweeney JA. Redundancy in measures of depression. *J Clin Psychol* 1988;44(3):372–4.
- Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry* 2012;72(7):595–603.
- George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. *Am J Psychiatry* 2011;168(4):356–64.
- Gratton G, Coles MG, Donchin E. A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 1983;55(4):468–84.
- Haller M, Donoghue T, Peterson E, Varma P, Sebastian P, Gao R, et al. Parameterizing neural power spectra. *bioRxiv* 2018:299859.
- Harmer CJ. Neural predictors of treatment response in depression. *Curr Behav Neurosci Rep* 2014;1(3):125–33.
- Hoy KE, Segrave RA, Daskalakis ZJ, Fitzgerald PB. Investigating the relationship between cognitive change and antidepressant response following rTMS: a large scale retrospective study. *Brain Stimul* 2012;5(4):539–46.
- Hyvarinen A. Fast and robust fixed-point algorithms for independent component analysis. *IEEE Trans Neural Netw* 1999;10:626–34.
- Hyvarinen A, Oja E. Independent component analysis: algorithms and applications. *Neural Netw* 2000;13:411–30.
- Insel TR, Wang PS. Rethinking mental illness. *JAMA* 2010;303(19):1970–1.
- Krepel N, Sack AT, Kenemans JL, Fitzgerald PB, Drinkenburg WH, Arns M. Non-replication of neurophysiological predictors of non-response to rTMS in depression and neurophysiological data-sharing proposal. *Brain Stimul: Basic, Trans, Clin Res Neuromodulat* 2018;11(3):639–41.
- Langguth B, Wiegand R, Kharraz A, Landgrebe M, Marienhagen J, Frick U, et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). *Neuro Endocrinol Lett* 2007;28(5):633–8.
- Love J, Selker R, Marsman M, Jamil T, Dropmann D, Verhagen J, et al. JASP: Graphical statistical software for common statistical designs. *Journal of Statistical Software* 2019;88(2):1–17.
- Nigbur R, Ivanova G, Stürmer B. Theta power as a marker for cognitive interference. *Clin Neurophysiol* 2011;122(11):2185–94.
- Onton J, Delorme A, Makeig S. Frontal midline EEG dynamics during working memory. *Neuroimage* 2005;27(2):341–56.
- Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, et al. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am J Psychiatry* 2001;158(3):405–15.
- Roelofs C, Krepel N, Corlier J, Carpenter L, Fitzgerald PB, Daskalakis Z, et al. Individual alpha frequency proximity associated with rTMS outcome: An independent replication study from the ICON-DB consortium. *Clinical Neurophysiology* 2021;132:643–649.
- Ruxton GD, Neuhäuser M. When should we use one-tailed hypothesis testing? *Methods Ecol Evol* 2010;1(2):114–7.
- Sauseng P, Hoppe J, Klimesch W, Gerloff C, Hummel FC. Dissociation of sustained attention from central executive functions: local activity and interregional connectivity in the theta range. *Eur J Neurosci* 2007;25(2):587–93.
- Scheeringa R, Bastiaansen MC, Petersson KM, Oostenveld R, Norris DG, Hagoort P. Frontal theta EEG activity correlates negatively with the default mode network in resting state. *Int J Psychophysiol* 2008;67(3):242–51.
- Tenke CE, Kayser J, Pechtel P, Webb CA, Dillon DG, Goer F, et al. Demonstrating test-retest reliability of electrophysiological measures for healthy adults in a multisite study of biomarkers of antidepressant treatment response. *Psychophysiology* 2017;54(1):34–50.
- Thase ME. Using biomarkers to predict treatment response in major depressive disorder: evidence from past and present studies. *Dialogues Clin Neurosci* 2014;16(4):539.
- van der Vinne N, Vollebregt MA, van Putten MJ, Arns M. Stability of frontal alpha asymmetry in depressed patients during antidepressant treatment. *NeuroImage: Clin* 2019;24:102056.
- Vinck M, Oostenveld R, Van Wingerden M, Battaglia F, Pennartz CM. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *Neuroimage* 2011;55(4):1548–65.
- Widge AS, Bilge MT, Montana R, Chang W, Rodriguez CI, Deckersbach T, et al. Electroencephalographic biomarkers for treatment response prediction in major depressive illness: a meta-analysis. *American Journal of Psychiatry* 2019;176(1):44–56.
- Widge AS, Bilge MT, Montana R, Chang W, Rodriguez CI, Deckersbach T, et al. Electroencephalographic biomarkers for treatment response prediction in major depressive illness: a meta-analysis. *Am J Psychiatry* 2018;176(1):44–56.
- Widge AS, Ellard KK, Paulk AC, Basu I, Yousefi A, Zorowitz S, et al. Treating refractory mental illness with closed-loop brain stimulation: progress towards a patient-specific transdiagnostic approach. *Exp Neurol* 2017;287:461–72.
- Zalesky A, Fornito A, Bullmore ET. Network-based statistic: identifying differences in brain networks. *Neuroimage* 2010;53(4):1197–207.